b) exciting the sample so as to generate signal from the bound labeled analyte; and

c) measuring the signal generated from the bound labeled analyte, thereby quantitative or qualitative determining the labeled analyte, wherein the determination of the labeled analyte occurs without physically separating unbound and bound labeled analyte.

REMARKS

New Claims

New claims 42-47 have been added. These claims further define the invention to include embodiments where the solid phase is coated with a quenching substance. Independent claim 46 is directed to embodiments of the invention where the solid phase is coated with a metal quenching substance. Independent claim 47 is directed to embodiments of the invention where the analyte is labeled. Support for the new claims is found in the specification and claims as originally filed, for example, at pages 10-13 and claim 18. None of these claims constitutes new matter. Accordingly, entry of these new claims is respectfully requested.

Amended Claims

Claims 2-7, 9-16, 19, 21, 23, and 33-36 have been amended. These amended clams further define specific embodiments of the claimed invention. None of the amendments constitutes new matter. Entry of the amended claims, and reconsideration of the application as amended, is respectfully requested.

Canceled Claims

Applicants have canceled claims 1, 8, 17, 18, 20, 22 and 37-41 without disclaimer. Applicants reserve the right to pursue these claims in a future application. Accordingly, any pending rejections are rendered moot as to these claims.

REJECTIONS

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 1-23 and 33-41 under 35 U.S.C. § 112, second paragraph, asserting that these claims are vague and indefinite for missing essential elements.

Applicants respectfully traverse this rejection. Applicants maintain that the claims as written are definite to one skilled in the art. Moreover, Applicants have added new claims 42-47 and amended claims 2-7, 9-16, 19, 21, 23, and 33-36 to further define the claimed invention without disclaiming subject matter or narrowing the scope of the claims. Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

Rejection Based On Hargreaves Under 35 U.S.C. § 102(e)

Claims 1-4, 6-14, 17-18, 20, 23 and 34-35 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Hargreaves (U.S. Patent No. 6,121,055). Applicants respectfully traverse this rejection.

The Examiner contends that Hargreaves discloses a two-phase assay system having an aqueous phase containing the analyte, reactants, label and primary layer which is on a solid phase (i.e., well of a microtiter plate). The Examiner asserts that Hargreaves uses the primary layer to separate bound from unbound label (i.e., fluorophores and laser type dyes). The Examiner then concludes that Hargreaves anticipates the present invention.

Applicants respectfully disagree. For a rejection to be sustained under § 102(e) each and every element of the claimed invention must be disclosed in the cited prior art reference. The present invention as claimed includes the quantitative or qualitative determination of an analyte using a solid phase coated with a quenching substance where there is no physical separation (washing, centrifugation, separation layers) of bound and unbound label.

Hargreaves discloses physical separation (i.e., washing, filtration, separation layers or centrifugation) of bound and unbound label. See, for example, col. 8,1:67 to col. 9, l: 2:

> The bound label may be eluted from the particles (such as with a sugar solution for glycosylated hemoglobin), prior to the absorbance measurement.

Hargreaves also discloses separating or filtering bound and unbound label by passing it through the primary layer at col. 11, l: 46-50:

> In heterogeneous binding assays, the primary layer serves to separate bound from unbound label by allowing the penetration of binding components without allowing the penetration of unbound label.

The primary layer that the Examiner asserts separates bound from unbound label, requires physical separation techniques such as centrifugation. See for example, col. 6 l: 39-48:

> For homogeneous assays, additional embodiments are employed. In one such embodiment, the density of the entire assay mixture may be greater than the density of the primary layer. Such an embodiment typically utilizes a barrier layer or primary layer which is in a solid or gel form during assay initiation, but which is displaced by the assay mixture during a subsequent **centrifugation step** (emphasis added).

Clearly Hargreaves calls for physical separation of bound and unbound label. Moreover, Hargreaves does not disclose coating a solid phase with a quenching substance. Accordingly, Hargreaves does not disclose each and every element of the claimed invention. Applicants respectfully request that this rejection under 35 U.S.C. § 102(e) be reconsidered and withdrawn.

Rejection Based On Te Koppele Under 35 U.S.C. § 102(e)

The Examiner rejects claims 1, 8-13, 17-18, 20, and 34-35 under 35 U.S.C. § 102(e) as being anticipated by Te Koppele (U.S. Patent No: 6,127,139). Applicants respectfully traverse this rejection.

The Examiner asserts that Te Koppele discloses a method for assaying an analyte (such as a proteolytic enzyme) in a system with two phases, the liquid phase contains the analyte and the solid phase has a fluorescence-quenched peptide with a specific enzymatic cleavage site. This peptide is cleaved if the analyte contains the proper enzyme, causing the fluorophore to be released, which produces the fluorescent signal. The Examiner asserts that this fluorescence-quenched peptide remains immobilized on the solid phase upon enzymatic cleavage. The Examiner then concludes that Te Koppele anticipates the present invention.

Applicants respectfully disagree. For a rejection to be sustained under § 102(e) each and every element of the claimed invention must be disclosed in the cited prior art reference. The present invention as claimed includes measuring the signal generated from the labeled reagent that is bound to the analyte in a system where the solid phase is coated with a quenching substance and there is no physical separation (washing, centrifugation, separation layers) of bound and unbound label.

Te Koppele discloses that the enzymatic cleavage site is always between the quencher and fluorophore. Accordingly, upon enzymatic cleavage, the flurophore is released and any signal generated is dependent on the cleavage of the peptide by the analyte, not on the binding of the label to the analyte. See for example, col. 3, l: 45-55. Thus, Te Koppele clearly does not disclose the presently claimed invention of the label binding to the analyte.

Moreover, Te Koppele discloses physical separation (i.e., washing) of bound and unbound label. See, for example, col. 1, l: 47-54:

> With the immobilized fluorescence-quenched substrates, e.g. on microtiter plates, the fluorescent fragments remain attached to the insoluble carrier after proteolytic cleavage.

> Thus, disturbing components of the reaction mixture (e.g. blood) can easily be **washed away**, providing a clean solution for use in the actual measurement. As a result, a more sensitive and reliable assessment of proteolytic enzyme activity is achieved (emphasis added).

Accordingly, Te Koppele does not disclose each and every element of the claimed invention. Applicants respectfully request that this rejection under 35 U.S.C. § 102(e) be reconsidered and withdrawn.

Rejection Based On Saunders Under 35 U.S.C. § 102(b)

Claims 1-2, 4,6, 8-13, 17-18, 20, and 34-35 are rejected under 35 U.S.C. 102 (b) as being anticipated by Saunders (U.S. Patent No. 5,674,699). Applicants respectfully traverse this rejection.

The Examiner asserts that Saunders discloses a method for qualitatively or quantitatively measuring an analyte in a sample by contacting the sample with reactants (particles and affinity reagent) to form a mixture, then fractionating the mixture to form two different phases including a solid phase (particle rich fraction) and a liquid phase (particle free fraction). The Examiner further asserts that Saunders discloses optically reading measurement signals from each of the phases while they are present in parallel within the carrier. The Examiner then concludes that Saunders anticipates the present invention.

Applicants respectfully disagree. For a rejection to be sustained under § 102(b) each and every element of the claimed invention must be disclosed in the cited prior art reference. The present invention as claimed includes the quantitative or qualitative determination of an analyte using a solid phase coated with a quenching substance where there is no physical separation of bound and unbound label.

Saunders discloses fractionation (i.e., physical separation) of the sample into a particle rich zone and a substantially particle free zone. See for example col. 16, l: 33-35. Moreover, Saunders discloses that the analyte acts as the quenching molecule. The label is inserted into the analyte, thus quenching the signal. See for example, col. 13, l: 24-26,

col. 22, l: 44-47 and Example 2.

Thus, Saunders does not disclose coating a solid phase with a quenching substance. Accordingly, Saunders does not disclose each and every element of the claimed invention. Applicants respectfully request that this rejection under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Rejection Based On Komives Under 35 U.S.C. § 102(b)

Claims 1-2, 4, 8-9, and 20 are rejected under 35 U.S.C. 102 (b) as being anticipated by Komives (U.S. Patent No. 5,510,247). Applicants respectfully traverse this rejection.

The Examiner asserts that Komives discloses a multiphase reaction system capable of measuring reaction products of an analyte by dynamic light scattering. Several embodiments are disclosed including fluorescence scanning of gels used in gene sequencing and fingerprint detection. The Examiner then concludes that Komives anticipates the present invention.

Applicants respectfully disagree. For a rejection to be sustained under § 102(b) each and every element of the claimed invention must be disclosed in the cited prior art reference. The present invention as claimed includes the quantitative or qualitative determination of an analyte using a solid phase coated with a quenching substance where there is no physical separation of bound and unbound label.

Komives discloses centrifugal systems that accomplish multiphase separation of products. See the summary of invention at col. 4, l: 33-36:

> Accordingly, **centrifugal systems** are provided which can accomplish a , multiphase reaction/separation of products or extraction/separation in a single-stage process. In these systems, centrifugal force maintains substantially separate phases in the vicinity of outlet port(s) of the system, as a result of differences in density between the phases. These systems provide the capability of continuous operation (emphasis added).

Moreover, Komives does not disclose coating a solid phase with a quenching substance. In fact, Komives does not mention quenching substances at all. In summary, Komives requires physical separation of bound and unbound label and does not disclose coating a solid phase with a quenching substance. Accordingly, Komives does not disclose each and every element of the claimed invention. Applicants respectfully request that this rejection under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejects claims 5, 15-16, 19, 21-22 under 35 U.S.C. § 103(a) as being unpatentable over Hargreaves in view of Dixon (U.S. Patent No. 5,381,224). Applicants respectfully traverse this rejection.

The Examiner contends that Hargreaves discloses a two-phase assay system having an aqueous phase containing the analyte, reactants, label and primary layer which is on a solid phase i.e., well of a microtiter plate. The Examiner asserts that Hargreaves uses the primary layer to separate bound from unbound label (i.e., fluorophores and laser type dyes). The Examiner concedes that Hargreaves fails to teach spatially staggered measurement of the signal and a plurality of measurement taken after excitation of the analyte with light. The Examiner combines Hargreaves with Dixon and remedies this defect and concludes that the present invention is obvious.

Applicants respectfully disagree. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488,20 USPQ2d 1438 (Fed. Cir. 1991).

As stated above Hargreaves discloses physical separation (i.e., washing, filtration, separation layers or centrifugation) of bound and unbound label. See, for example, col. 8, l: 67 to col. 9, l: 2, col. 11, l: 46-50, and col. 6, l: 39-48. Further, Hargreaves does not disclose coating a solid phase with a quenching substance. Accordingly, Hargreaves does not teach or suggest the presently claimed invention.

Dixon discloses scanning optical imaging of macroscopic specimens, which is said to allow both confocal and non-confocal imaging in reflected light, as well as photo-luminescence, fluorescence and other contrast mechanisms. See col. 3, l:10-20. Dixon does not teach or suggest the quantitative or qualitative determination of an analyte using a solid phase coated with a quenching substance where there is no physical separation of bound and unbound label. In fact, Dixon does not mention quenching substances at all. Since Dixon does not teach or suggest the presently claimed invention, this reference cannot render the present invention obvious.

Moreover, there is simply no mention, teaching or suggestion in Dixon and/or Hargreaves of an assay where the solid phase is coated with a quenching substance and there is no physical separation (i.e., washing, centrifugation) of bound and unbound label. Accordingly, one skilled in the art would certainly not look to these references to get the claimed invention. Thus, there is no motivation to combine these references to get the claimed invention. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

19358.1
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Stemmler et al. Docket No.: 13424

Serial No.: 09/492,214 Group Art Unit: 1641

Date Filed: January 27, 2000 Examiner: Gabel, Gailene

For: Quantitative Determination Of Analytes In A Heterogeneous System

Customer No.:

23719
PATENT TRADEMARK OFFICE

Kalow & Springut LLP
488 Madison Avenue, 19th Floor
New York, New York 10022

October 9, 2002

Assistant Commissioner for Patents
Washington, D.C. 20231

MARKED UP CLAIMS

Dear Sir:

In accordance with 37 CFR §1.121 (c) the following marked up claims are submitted to accompany the amendment filed concurrently for the application identified above.

IN THE CLAIMS

Please amend the following claims:

2. (Amended) The method according to Claim [1] 44 in which the method is an affinity assay.

3. (Amended) The method according to Claim [1] 42 in which the analyte comprises a nucleic acid.

4. (Amended) The method according to Claim [1] 44 in which the method is an immuno-affinity assay.

5. (Amended) The method according to Claim [1] 42 in which the analyte determination occurs in a volume [in which the detection reaction occurs is] of less than 1 µl.

6. (Amended) The method according to Claim [1] 44 in which the method is a competitive assay.

7. (Amended) The method according to Claim [1] 44 in which the method is a sandwich assay.

9. (Amended) The method according to Claim [8] 42 in which the measurement signal is generated by irradiation excitement of the bound labeled reagent.

10. (Amended) The method according to Claim [8] 42 in which the labeled reagent is a fluorescent labeled reagent.

11. (Amended) The method according to Claim [1] 42 in which the sample is in a [first phase of said at least two different phases is a solid phase and a second phase of said at least two different phases is a] liquid phase.

12. (Amended) The method according to Claim [1] 42 in which [one of said at least two different phases is a solid phase, and] the solid phase is formed on a wall of a well in a sample carrier.

13. (Amended) The method according to Claim 12 in which the carrier is [provided in a form of] a micro-titre or nano-titre plate.

14. (Amended) The method according to Claim 12 in which [a] the well has a quadratic, cylindrical, truncated pyramid or truncated cone shape.

15. (Amended) The method according to Claim 12 in which [a] the well has an aperture area and a floor area, the aperture area being smaller than the floor area.

16. (Amended) The method according to Claim 15 in which [a] the well has a truncated pyramid or truncated cone shape.

19. (Amended) The method according to Claim [1] 42 in which [at least one] the measurement signal is obtained by spatially staggered measurement.

21. (Amended) The method according to Claim [20] 42 in which a [stimulating] light beam is used to excite [stimulate] the sample, said [stimulating] light beam having a diameter [in the sample volume] of less than 40 μm.

23. (Amended) The method according to Claim [20] 21 in which a laser provides the [stimulating] light beam [and florescence of the label excited by the laser beam is used to provide a measurement signal].

33. (Amended) The method according to Claim [20] 5 in which the volume [in which the detection reaction occurs] is in the range of 50 to 100 nl.

34. (Amended) The method according to Claim [12] 13 in which the sample carrier is [provided in a form of] a nano-titre plate.

35 (Amended) The method according to Claim [18] 42 in which the quenching substance is a metal, dye or fluorescence-quenching substance.

36. (Amended) The method according to Claim [20] 23 in which the [stimulating] light beam [in the sample volume] has a diameter of about 20 μm.

Respectfully submitted,

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